

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75285

APPROVAL LETTER

15-785 95

L. Perrigo
Attention:

[illegible]

This is in reference to your abbreviated new drug application dated December 19, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cimetidine Tablets USP, 200 mg.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted Over-The-Counter (OTC) labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cimetidine Tablets USP, 200 mg to be bioequivalent to the listed drug (Tagamet HB®, 200 Tablets, of SmithKline Beecham Consumer Healthcare). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

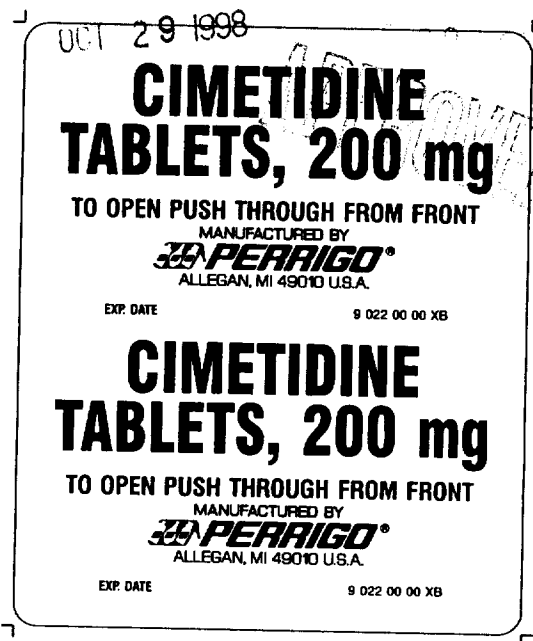
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75285

DRAFT FINAL PRINTED LABELING

Final Printed Labeling
Blister Strip Back
ANDA 75-285
Cimetidine Tablets, 200 mg



{Lot number and expiration date
will appear on strip.}

Final Printed Labeling
Carton
ANDA 75-285
Cimetidine Tablets, 200 mg

marg

EFB182

OCT 29 1988



Read the directions and warnings before taking this medication.
Do not discard carton, contains important information.

- WARNINGS:**
- Allergy Warning: Do not use if you are allergic to cimetidine or other acid reducers.
 - Consult your doctor if you are taking theophylline (oral asthma medicine), warfarin (blood thinning medicine), or phenytoin (seizure medicine) before taking this product. If you are not sure whether your medication contains one of these drugs or have any other questions about medicines you are taking, call your doctor or a health care professional.
 - Do not take the maximum daily dosage for more than 2 weeks continuously except under the advice and supervision of a doctor.
 - If you have trouble swallowing, or persistent abdominal pain, see your doctor promptly. You may have a serious condition that may need a different treatment.
 - As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.
 - Keep this and all drugs out of the reach of children.
 - In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

- DIRECTIONS:**
- For relief of symptoms swallow 1 tablet with a glass of water.
 - This product can be used up to twice daily (up to 2 tablets in 24 hours).
 - This product should not be given to children under 12 years old unless directed by a doctor.

USES: Relieves heartburn, acid indigestion, and sour stomach.
ACTIVE INGREDIENT: Cimetidine 200 mg per tablet. **PURPOSE:** Acid Reducer.

This product relieves heartburn, acid indigestion and sour stomach when used as directed. It contains the same ingredient found in prescription strength Tagamet®. This product reduces the production of stomach acid.

INACTIVE INGREDIENTS: Com Starch, Hydroxypropyl Methylcellulose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80, Povidone, Sodium Lauryl Sulfate, Sodium Starch Glycolate, Titanium Dioxide.

Store at room temperature (59-86°F).

CIMETIDINE
TABLETS, 200 mg

EACH TABLET INDIVIDUALLY SEALED
IN A BLISTER PACK. DO NOT USE IF
BLISTER OR FOIL IS BROKEN.

CIMETIDINE TABLETS, 200 mg

Reduces the Production of Stomach Acid

Now Available Without A Prescription

COMPARE TO THE ACTIVE INGREDIENT OF TAGAMET HB 200

Relieves heartburn, acid indigestion,
and sour stomach.

One
Tablet
Dose

6 COATED TABLETS (6 DOSES)

CIMETIDINE
TABLETS, 200 mg

MANUFACTURED BY
PERRIGO
ALL LECAN, MI 48010 U.S.A.

302291FAA

302291FAA

3 022 91 FAA

OPEN OTHER END

CONVENIENT RECLOSING TAB

{Lot number and expiration
date will appear on carton.}

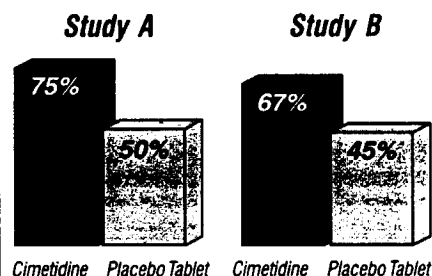
Non-Prescription Cimetidine Tablets, 200 mg Acid Reducer For Heartburn.

The active ingredient in this product is the same medicine doctors have prescribed over 200 million times. And now that same medicine is available without a prescription for heartburn.

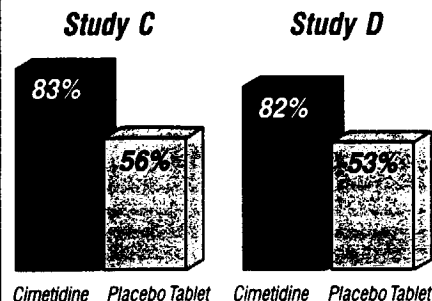
This product reduces the production of stomach acid that can cause heartburn.

In clinical studies, cimetidine was significantly better than placebo tablets in relieving and preventing heartburn symptoms.

Percent of Heartburn Episodes Relieved



Percent of Patients with Reduction of Heartburn Symptoms



DRUG INTERACTION WARNINGS:

This product affects some prescription medicines causing slightly higher levels of those medicines in the blood. Higher blood levels could lead to side effects in rare situations. If you currently take **Theophylline** (oral asthma medicine), **Warfarin** (blood thinning medicine) or **Phenytoin** (seizure medicine), consult your doctor before taking this product.

Brand names of some medicines which contain one of these ingredients include:

THEOPHYLLINE	THEO-DUR® Theochron® Slo-Bid® Uniphyll® Theo-24®
WARFARIN	Coumadin®
PHENYTOIN	Dilantin®

There may be other medicines that contain one of these ingredients. If in doubt about this or about possible effects of this product on any other medicines you are taking, talk to your doctor.

OTHER INFORMATION:

Tips for Managing Heartburn

- Do not lie flat or bend over soon after eating.
- Do not eat late at night, or just before bedtime.
- Certain foods or drinks are more likely to cause heartburn, such as, rich, spicy, fatty, and fried foods, chocolate, caffeine, alcohol, even some fruits and vegetables.
- Eat slowly and do not eat big meals.
- If you are overweight, lose weight.
- If you smoke, quit smoking.
- Raise the head of your bed.
- Wear loose fitting clothing around your stomach.

ACTIVE INGREDIENT: Cimetidine 200 mg per tablet. **PURPOSE:** Acid Reducer.

USES: - Relieves heartburn, acid indigestion, and sour stomach.

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READ
THE LABEL

Read the directions and warnings before taking this medication.

MANUFACTURED BY
PERRIGO®
ALLEGAN, MI 49010 U.S.A.

Rev. Date 08/98

496073

Final Printed Labeling
Package Insert
ANDA 75-285
Cimetidine Tablets, 200 mg

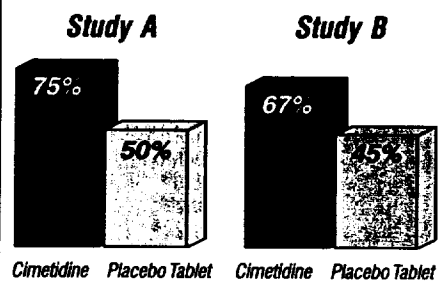
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Cimetidine Tablets,
200 mg
Acid Reducer
For Heartburn.**

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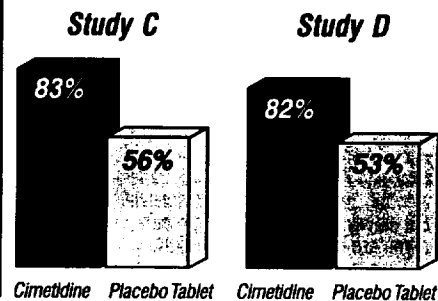
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**Percent of Patients
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MANUFACTURED BY
PERRIGO®
ALLEGAN, MI 49010 U.S.A.

Rev. Date: 08/98
496073

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75285

CHEMISTRY REVIEW(S)

DIVISION REVIEW SUMMARY

ANDA: 75-285

FIRM: L. Perrigo Company

DOSAGE FORM: Tablets

STRENGTH: 200 mg

DRUG: Cimetidine

CGMP STATEMENT/EIR UPDATE STATUS:

Acceptable, June 22, 1998.

manufacturer of the drug substance, acceptable.

BIO STUDY INFORMATION:

The Division of Bioequivalence has completed their review, and has indicated the dissolution testing as specified in the USP has been incorporated by the firm into the stability and quality control program for testing as described in the finished drug product and stability specification included in the ANDA. See bio review dated 4/27/98

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S)

Validation report for the assay of cimetidine tablets 200 mg is presented and includes the stability indicating nature of the assay method and forced degradation, as follows:

- a. Chromatographic conditions (pp. 366 -367)
- b. Preparation of the recovery-linearity samples and standard (pp. 368 & 369)
- c. Single analyst and analyst to analyst precision (p. 369).
- d. Preparation of the hydrogen peroxide, sulfuric acid, hydrochloric acid and sodium hydroxide degraded samples (pp. 370 & 371).
- e. Injection of a three month accelerated stability project 10951 (lot No. 5Z0787) was prepared according to the "Preparation of the sample and standard solutions" (p. 369)- (p. 371) and system suitability (p. 371).

Results: The method for determination of cimetidine in cimetidine tablets is proven accurate and precise by peak area for the quantitation of the drug substance.

The average percent recovery from the base mix ranged from %, average of 100.5%. The method demonstrate specificity for cimetidine (pp. 375-376)

The sample assay precision was determined to be 0.6% RSD (p. 376).

The single analyst precision, determined over three days using different columns was % (p. 377)

The analyst to analyst precision of the assay was % (p. 377)

The system suitability parameters and the recovery of cimetidine in dissolution medium data are presented (p. 378).

Related scans are presented (pp. 381 -385).

The firm states that the assay method validation for the drug substance and for the inactive ingredients are compendial and therefore validation is not required (p. 490). See also methods verification report as per Chicago District dated 3/19/98.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?

Yes, as per the following information: The executed batch was partially packaged. The firm states that the amount was in excess of units, as follows (p. 169):

Packaging lot:	No. of tablets:
7T3048	
7T3049	
7T3050	

-
Total

The firm requests approval of "only the components used in packaging lot No. 7T3048 (10 mil PVC film with UV inhibitor)."

Packaging lot No. 7T3048 was packaged using Perrigo's material code 496315: Penthapharm Ph 170/04-10100 with UV inhibitor, lot No. 1509557 (p. 227).

Stability test, procedure and specifications are included as follows:

Test	Procedure	Specifications
Description	Method 596 Compare to ID sample	A white film-coated oval tablet with the logo "L022" debossed into one face
Container/closure	564	Passes
Assay (cimetidine)	1409	mg/tablet
Tablet dissolution	1410	NLT % (Q) in 15 minutes
Chromatographic impurities:	1421	
Sulfoxide impurity	-----	NMT %
Amide impurity	-----	NMT %
Guanidine impurity	-----	NMT %
Other unknown impurities	-----	NMT %
Total impurities		Total NMT %.

Stability data, for both: the market packaging configuration 6 ct. strip (blister) and the bulk packaging configuration (plastic bag in drum), 1, 2 and 3 months data, stored at accelerated conditions: 40° C/75% RH, and 3 month at room controlled temperature 25° - 30° C (pp. 394 - 397).

Post approval stability commitment and stability studies presented are adequate (pp. 398 - 400).

The firm provided updated stability test results through 12 months for the bioequivalence batch, with their Facsimile amendment dated August 19, 1998.

The stability data, and the test results for the batch 7T3048, at 3, 6, 9 and 12 months, 6 ct packaged mil PVC w/UV inhibitor film and 1 mil push through foil, presented are acceptable (pp. 7 - 9, enclosure 3).

LABELING:

Acceptable. See review dated 9/24/98.

STERILIZATION VALIDATION (IF APPLICABLE)

N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?)

Bio-batch's bulk final yield was reported as units.

It is relevant to mention that only a partial of the batch was packaged in the proposed marketing blister (10 mil PVC film with UV inhibitor), foil system: tablets successfully packaged.

10/15/98 DMF Cimetidine, found adequate on

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

Is the same batch No. 7T3048.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS
BIO/STABILITY?

Only one batch size: units, is proposed by the firm. "The batch size may be increased in accordance with Policy and Procedure Guide 22-90."

The manufacturing process is the same as the bio/stability batch.

RECOMMENDATION:

Issue an approval letter

SIGNATURE

A. Croft

DATE:

September 10, 1998

APPEARS THIS WAY
ON ORIGINAL

**APPEARS THIS WAY
ON ORIGINAL**

1. Components/composition:

Component	Mg/Tablet	Quantity/ units (Kg)
✓Cimetidine USP		
✓Microcrystalline Cellulose NF		
✓Pregelatinized Starch (Corn) NF		
✓Sodium Starch Glycolate NF		
✓Povidone (K-90) USP		
✓Sodium Lauryl Sulfate NF		
✓Magnesium Stearate NF		
Purified Water USP	*	*
Coating Components (Opadry YS-1-7003):		(5.42 Kg)
✓Hydroxypropyl Methyl Cellulose USP		
✓Titanium Dioxide USP		
✓Polyethylene Glycol NF		
✓Polysorbate 80 NF		
Total weight		kg

*: Purified Water USP for processing only. Not present in the final product.

2. The firm states that the manufacturing process is limited to a specific size due to the capacity of the granulation equipment. Consequently two granulation batches are manufactured. The ingredients that are in excess of the theoretical quantities are "due to the granulation amount which is manufactured but not used in the cimetidine tablet manufacturing order. The granulation batch size is larger than the minimum required size in order to allow some variation in the yield of this process".

**APPEARS THIS WAY
ON ORIGINAL**

ANDA 75-285

NAME AND ADDRESS OF APPLICANT:

L. Perrigo Company
Mr. Brian R. Shuster
117 Water Street
Allegan, MI 49010

PURPOSE OF AMENDMENT/SUPPLEMENT

Response to our Facsimile deficiencies dated August 3, 1998

DATE(S) OF SUBMISSION(S)

Original:	December 19, 1997
FDA acknowledge receipt:	December 6, 1998
Acceptable for filing:	December 29, 1998
Detroit District (samples for MV):	February 6, 1998
Detroit District (MV, acceptable):	March 19, 1998
Facsimile deficiencies:	August 3, 1998
Facsimile amendment:	August 19, 1998
Facsimile amendment:	September 18, 1998

PHARMACOLOGICAL CATEGORY

TRADE NAME

Histamine H²-receptor antagonist

N/A

NONPROPRIETARY NAME

Cimetidine

DOSAGE FORM

POTENCY

RX OR OTC

Tablet

200 mg

Rx

SAMPLES

RELATED IND/NDA/DMF

STERILIZATION

N/A

See chem/review #1

N/A

LABELING

Acceptable. Se review dated 9/24/98

*Signed
casy*

BIOEQUIVALENCY STATUS

As indicated by the Division of Bioequivalence the dissolution testing as specified in the USP is incorporated into the stability and quality control program for testing as described in the finished drug product and stability specification included in the ANDA.

ESTABLISHMENT INSPECTION

Acceptable, June 22, 1998.
 manufacturer of the drug substance, acceptable,
2/6/98.

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

Deficiency:

We are cognizant of your in-process specifications, method and test results for the tablet mix (apparently the final blend) and for the release of the cores, however we need to ascertain that these laboratory controls are included as in-process controls for the commercial batches. Please revise and/or submit your commitment.

Response:

The firm commits to test the commercial batches according to the in-process specifications once approved in the ANDA. "The tablet mix does represent testing to be performed on the final blend prior to compression of the cores. Acceptable.

Deficiency:

In relation to your COA for cimetidine drug substance your specification for Polymorph B is NMT %. In order to ascertain that the total of all others polymorphs are less than %, the specification should be changed to polymorph A NLT %.

Response:

The specification for cimetidine USP, drug substance has been revised to add a specification for the content

of Polymorph A. The revised specification is appended (pp. 5 & 6, enclosure 2) and includes the following limits:

I.R. Polymorph A (Procedure 1321) NLT %

I.R. Polymorph B (Procedure 1321) NMT %

Acceptable.

PACKAGING

Deficiency:

You presented a batch yield after packaging as follows:

Pkg Lot No.	kg Issued	Tablets/kg	Tbs/Pkg Lot	Percentage
7T3048	19 kg			%
7T3049	19 kg			%
7T3050	19 kg			%
Total packaged				%
Bulk stability	25.2 kg			%
Bulk storage	205.1 kg			%
Total:				%

It is noted that the number of tablets per packaged batch reported (p. 169) differs from the tabulated above (p. 271):

Packaging lot	No. of tablets:
	(Page 169) (Page 271)
7T3048	
7T3049	
7T3050	

Total:

Please clarify and/or revise and submit.

Response:

The firm explains that the batch yields reported represent the yield calculations to account for the product produced in manufacturing. The number of tablets per packaged batch is the actual number of successfully packaged tablets and does not include the packaging process losses and thus the numbers reported on page 169 and 271 under the individual packaging lot numbers differ by the amount of process losses.

A table and an explanation detailing the reconciliation of the packaged product is presented (p. 2, covering letter). Acceptable.

STABILITY

Deficiency:

We acknowledge your request for approval of "only the components used in packaging units) lot No. 7T3048, 10 mil PVC", item No. 496315: Penthapharm Ph 170/04-10100 with UV inhibitor. Please advise us of the final disposition of the drug product packaged under lots No. 7T3049 and 7T3050.

Response:

The drug product produced under packaging lots 7T3049 and 7T3050 is currently maintained in inventory and these lots are included in the real time stability testing program. They will be maintained until such a time that the stability studies are concluded, afterwards they will be disposed of following appropriate disposition procedures.

The firm takes "this opportunity to provide updated stability test results through 12 months for the bioequivalence batch.

Comments:

The explanation of the final disposition of the drug product packaged under lots No. 7T3049 and 7T3050 is acceptable.

The stability data, and the test results for the batch 7T3048, at 3, 6, 9 and 12 months, 6 ct packaged mil PVC w/UV inhibitor film and 1 mil push through foil, presented are acceptable (pp. 7 - 9, enclosure 3).

REMARKS AND CONCLUSION

Deficiency:

You state in the Form FDA 356h that the "Reason for Submission" is : "Alternate source of the drug substance". Please revise and submit.

Response:

The form FDA 356h has been revised and a corrected copy is enclosed in Attachment 1.

Comments:

It is noted that attachment 1 is a blank form, however page 1, is the correct revised form. Acceptable.

CONCLUSION

The amendment is acceptable.

RECALLS

N/A

Reviewer

A. Casloru

Date Completed

September 10, 1998

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75285

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-285

APPLICANT: L. Perrigo Company

DRUG PRODUCT: Cimetidine 200 mg tablet

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/s/

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Cimetidine
200 mg tablet
NDA #75-285
Reviewer: J. Lee
75285SD.D97
75285STA.498

L. Perrigo Company
Allegan, Michigan
Submission date:
December 19, 1997
April 22, 1998

**Review of Fasted and Fed in-vivo Bioavailability Studies,
and Dissolution Testing Data**

Objective:

To determine the relative bioavailability of two 200 mg cimetidine tablet formulations (OTC) after administration of single doses to healthy male subjects under both fasted and fed conditions.

Fasted Study

Study Design:

The clinical study (#116-24-11232) was conducted at _____, Principal Investigator, and _____ under the supervision of _____, Project Director.

Twenty-six healthy male volunteers between the ages of 18-45 years and within 15% of ideal body weight for his height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination and clinical laboratory tests [hematology, serum chemistry, urinalysis, urine drug screen and HIV 1 test].

Those with any of the following conditions were excluded:

History of:

- asthma, peptic or duodenal ulcers, diabetes, psychiatric illness
- organ-system disorders
- alcohol or drug abuse
- allergy to cimetidine or any other histamine H₂ antagonist

Rx and OTC medications were not allowed within 14 and 7 days, respectively, of the first drug administration. There was to be no alcohol consumption for at least 48 hours prior to drug

administration. Subjects who had taken aspirin, acetaminophen or caffeine within 24 hours before dosing were not allowed to participate in the study.

The study was designed as a randomized, two-treatment, two-period, two-sequence crossover study with a 7 day washout period between dosings. Treatments consisted of a single 200 mg dose of the following:

- A. Cimetidine
200 mg tablet, batch #7S0768 (mfg.); batch #7T3048 (pkg.)
L. Perrigo Company
expiry date: May, 1999
- B. Tagamet® HB 200
200 mg tablet, batch #7C31C042
SmithKline Beecham
expiry date: March, 1999

Twenty-six subjects were dosed according to the following schedule:

	Period I 07/19/97	Period II 07/26/97
sequence I	A	B
sequence II	B	A
sequence I - subj. # 2, 4, 5, 8, 9, 12, 14, 15, 18, 19, 21, 24, 25		
sequence II - subj. #1*, 3, 6, 7, 10, 11, 13, 16, 17*, 20, 22, 23, 26		

*Subjects #1 and 17 did not return for period II for personal reasons. Twenty-four subjects completed the study.

After an overnight fast, subjects were given a 200 mg dose of cimetidine with 240 ml of water. Fasting continued for 5 hours post-dose. Blood samples (10 ml) were drawn in Vacutainers without anticoagulant at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 7, 8, 9, 10 and 12 hours. All sampling deviations are noted on Table 3 of the clinical summary. All deviations were ≤ 2 minutes of the scheduled sampling time and are considered insignificant.

The samples were cold centrifuged for 30 minutes and the serum transferred to polypropylene tubes and stored at -20°C pending analysis.

Four subjects reported experiencing a total of 6 adverse events, only three of which were judged to have been possibly related to the study medication. All were mild in severity. None required medication. The adverse events summary is attached.

No deviations from protocol were reported.

Analytical:

The serum samples were assayed for cimetidine by a method (using UV detection) developed by Sample preparation consisted of a pH adjustment, extraction with organic solvent, evaporation to dryness, and reconstitution. The resulting solution was then chromatographed on an

Quantitation of drug levels was based on peak height ratios of cimetidine to internal standard (N-propionylprocainamide) vs nominal standard concentration, using a linear least squares fit weighted by $1/\text{conc}^2$.

Standards were prepared in chromatographically screened serum in the concentration range of mcg/ml (7 points) for the calibration curve. The sensitivity of the assay was chosen at mcg/ml, the concentration of the lowest non-zero standard. Sample concentrations below this value were reported as zero.

The coefficient of determination (r^2) was ≥ 0.98382 for the standard curves. The coefficient of variation for the standards ranged from 1.24% (at 0.100 mcg/ml; n=25) to 4.31% (at 10.0 mcg/ml; n=25). There was one rejected standard curve value in all analytical runs.

The precision of the assay was monitored by the quality control samples that were run in duplicate with each group of samples. This data showed:

<u>QC Value</u>	<u>Mean</u>	<u>%CV</u>
0.200 mcg/ml (n=50)	0.189	4.06
2.00 mcg/ml (n=50)	1.92	4.64
6.00 mcg/ml (n=49)	6.03	4.06

Stability data submitted with the study showed no decline in cimetidine serum concentrations [at 0.200 and 6.0 mcg/ml; n=10] after a 32 day period for samples stored under frozen (- 20°C) conditions, covering the length of the study. In a separate studies, stability samples showed:

<u>Sample Conc.</u>	<u>freeze-thaw (%CV)</u> 3 cycles	<u>24 hr @ RT (%CV)</u>
0.250 mcg/ml (n=3)	0.261 mcg/ml (1.10)	0.254 mcg/ml (1.24)
5.00 mcg/ml (n=3)	5.03 mcg/ml (1.43)	4.84 mcg/ml (0.406)

Recovery data for cimetidine showed the following:

55.4% at 0.100 mcg/ml (CV=7.37%; n=7)
53.8% at 1.00 mcg/ml (CV=4.18%; n=7)
54.3% at 5.00 mcg/ml (CV=8.40%; n=7)

Recovery data for the internal standard:

98.8% at 25.0 mcg/ml (CV=1.76%; n=7)

Zero hour samples showed no quantifiable interference at the retention time of the drug peak/IS.

Data Analysis:

Serum data was analyzed by an analysis of variance procedure (SAS, version 6.11) and the F-test to determine statistically significant ($p < 0.05$) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters and serum level concentrations at each sampling time. Of the original twenty-six subjects enrolled in the study, two did not complete the crossover; twenty-four datasets were analyzed.

Results:

No statistically significant differences were found in the major pharmacokinetic indices, neither on the original nor on the ln-transformed scale. No sequence effects were observed for the same indices. There was a % difference between the test and reference formulations for serum levels of cimetidine in AUCs. The Perrigo product produced a % higher C_{max} than the SmithKline Beecham product. The % shortest confidence intervals for cimetidine, using least squares means, are presented below:

<u>90% CI</u>		
original scale	AUC _{0-t} (n=24)	[99; 108]
	AUC _{inf} (n=24)	[100; 108]
	C _{max} (n=24)	[100; 116]
ln-transformed scale	AUC _{0-t} (n=24)	[99; 108]
	AUC _{inf} (n=24)	[100; 108]
	C _{max} (n=24)	[101; 117]

Mean serum level data and pharmacokinetic summary are attached.

Fed Study

Study Design:

The clinical and analytical facilities for this study were the same as that employed in the fasted

study. The inclusion and exclusion criteria for subject selection were also the same.

The study (#116-24-11233) was a randomized, open-label, two treatment, two period, two sequence crossover. Treatments consisted of the same two batches of test and reference products (used in the fasted study). A 7 day washout period separated the dosings.

Twenty-six subjects were dosed according to the following regimen:

	Period I 07/26/97	Period II 08/02/97
sequence I	A	B
sequence II	B	A

sequence I - subj. # 2, 3, 6, 8, 10, 11, 14*, 16, 17, 19, 22, 24, 25

sequence II - subj. #1, 4, 5, 7, 9, 12, 13, 15, 18, 20*, 21, 23, 26

*Subject #14 was withdrawn from the study prior to period II for a positive drug screen and subject #20 failed to return for period II for personal reasons.

After an overnight fast, subjects were served a standard breakfast* 35 minutes before dosing (entire meal to be consumed in 30 minutes). Blood samples (10 ml) were drawn in Vacutainers without anticoagulant at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10 and 12 hours. All sampling deviations are noted on Table 3 of the clinical summary. All deviations were within 2 minutes of the scheduled sampling time.

*standard breakfast:

- 1 buttered English muffin
- 1 fried egg
- 1 slice of American cheese
- 1 slice of Canadian bacon
- 1 serving of hash brown potatoes
- 6 fl oz of orange juice
- 8 fl oz of whole milk

There were no adverse events or protocol deviations reported for this study.

Analytical:

The analytical method and validation was the same as that used in the fasted study.

The standard curve summary for this fed study showed a coefficient of determination (r^2) of ≥ 0.99039 . The coefficient of variation for the standards ranged from 1.99% (at 0.100 mcg/ml; n=26) to 4.99% (at 0.250 & 0.500 mcg/ml; n=26). There was no rejected standard curve value in all the runs.

The quality control samples were run in duplicate with each group of samples; the summary is presented below:

<u>QC Value</u>	<u>Mean</u>	<u>%CV</u>
0.200 mcg/ml (n=49)	0.195	5.37
2.00 mcg/ml (n=51)	0.507	6.32
6.00 mcg/ml (n=51)	1.98	7.70

Long-term stability data submitted with this study showed no decline in cimetidine serum concentrations [at 0.200 and 6.0 mcg/ml; n=12] after a 44 day period for samples stored under frozen (- 20°C) conditions, covering the length of the study. The freeze-thaw and in-process stability data and recovery data are the same as reported in the fasted study review.

Zero hour samples showed no quantifiable interference at the retention time of the drug peak/IS.

Data Analysis and Results:

Means, standard deviations and CV%s were calculated for AUC_{0-t} , AUC_{inf} , C_{max} , t_{max} , kel , $t_{1/2}$ and concentrations at each sampling time point (see attached table). Areas under the curve showed $\leq 2\%$ difference for T/R (fed) and a 7.0% difference in C_{max} ratios. The results are summarized in appended tables.

	<u>T/R</u>
AUC_{0-t}	0.98
AUC_{inf}	0.98
C_{max}	0.93

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using the current USP dissolution method. The resultant summaries are attached.

Content Uniformity:

The assay for content uniformity for 10 dosage units of the Perrigo product was 101% of label claim; range = 100 - 103% (1.0% CV); for Tagamet® HB 200 the C.U. was 100% of label claim - range = 98.5 - 102.5% (1.2% CV).

Batch Size:

The batch size for the bio-batch of Perrigo's 200 mg cimetidine was dosage units.

Comment:

1. The results of the fasted and fed bio-studies are acceptable.

Recommendation:

1. The bioequivalence studies (fasted and fed) conducted by for L. Perrigo Company on its cimetidine 200 mg tablet, batch #7S0768 (mfg), comparing it to Tagamet® HB 200 mg tablet has been found acceptable by the Division of Bioequivalence. The study demonstrates that Perrigo's 200 mg cimetidine tablet is bioequivalent (under fasted and fed conditions) to the reference product, Tagamet® HB 200 mg tablet manufactured by SmithKline Beecham.
2. The in-vitro dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water @ 37°C using USP XXIII apparatus I (basket) at 100 rpm. The test product should meet the following specification:

Not less than % of the labeled amount of the drug
in the tablet is dissolved in 15 minutes.

3. From the bioequivalence viewpoint the firm has met the requirements of in-vivo bioavailability and in-vitro dissolution testing and the application is acceptable.

/S/ 4/27/98

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

Concur: /S/ Date: 4/27/98

Dale Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/04-16-98

cc: NDA #75-285 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File,
Division File

[illegible]

#116-24-11232
 Bioavailability of Cimetidine 200 mg Tablets
 Cimetidine Serum Levels ($\mu\text{g/mL}$) After Single 200 mg Dose

Serum Cimetidine Parameter Means by Drug Treatment

fasted

Concentration/ Parameter	Perrigo				SmithKline Beecham			
	N	Mean	Std Dev	%CV	N	Mean	Std Dev	%CV
0 hr	24	0.00000	0.00000	.	24	0.00000	0.00000	.
0.25 hr	24	0.01321	0.04796	363.1	24	0.03071	0.07785	253.5
0.5 hr	24	0.43992	0.31902	72.5	24	0.47083	0.29812	63.3
0.75 hr	24	0.72004	0.35273	49.0	24	0.69342	0.32803	47.3
1 hr	24	0.79892	0.30217	37.8	24	0.69275	0.24225	35.0
1.25 hr	24	0.74792	0.22855	30.6	24	0.71267	0.24718	34.7
1.5 hr	24	0.77350	0.20917	27.0	24	0.73271	0.24755	33.8
1.75 hr	24	0.78438	0.20042	25.6	24	0.74650	0.21733	29.1
2 hr	24	0.80621	0.20706	25.7	24	0.79425	0.17095	21.5
2.33 hr	24	0.78967	0.21191	26.8	24	0.79333	0.14201	17.9
2.67 hr	24	0.71767	0.16446	22.9	24	0.72763	0.12807	17.6
3 hr	24	0.69871	0.16763	24.0	24	0.66683	0.13597	20.4
3.5 hr	24	0.59967	0.13764	23.0	24	0.57633	0.14735	25.6
4 hr	24	0.51425	0.10108	19.7	24	0.49763	0.12115	24.3
5 hr	24	0.37492	0.08469	22.6	24	0.37063	0.09916	26.8
6 hr	24	0.26083	0.05584	21.4	24	0.25167	0.07137	28.4
7 hr	24	0.19300	0.04585	23.8	24	0.18213	0.06514	35.8
8 hr	24	0.13950	0.05379	38.6	24	0.11896	0.07554	63.5
9 hr	24	0.08208	0.06638	80.9	23	0.07309	0.06810	93.2
10 hr	24	0.03396	0.05431	159.9	24	0.03300	0.05282	160.1
12 hr	24	0.00000	0.00000	.	24	0.00000	0.00000	.
AUC 0-T								
($\mu\text{g}\cdot\text{hr/mL}$)	24	3.80850	0.69250	18.2	24	3.67171	0.72176	19.7
Ln AUC 0-T	24	1.32091	0.18636	14.1	24	1.28225	0.19614	15.3
AUC 0-Inf								
($\mu\text{g}\cdot\text{hr/mL}$)	24	4.21583	0.75331	17.9	24	4.05721	0.73946	18.2
Ln AUC 0-Inf	24	1.42303	0.18354	12.9	24	1.38475	0.18103	13.1
Cmax ($\mu\text{g/mL}$)	24	1.05575	0.20935	19.8	24	0.97563	0.21916	22.5
Ln Cmax	24	0.03570	0.19645	550.4	24	-0.04852	0.22260	-459
Tmax (hr)	24	1.48208	0.68160	46.0	24	1.63833	0.68696	41.9
Rate Constant	24	0.30465	0.06443	21.1	24	0.31488	0.06131	19.5
Half-Life (hr)	24	2.37213	0.49747	21.0	24	2.28871	0.47770	20.9
Cmax/ AUCinf	24	0.25345	0.04693	18.5	24	0.24401	0.05445	22.3
Ln (Cmax/AUCinf)	24	-1.38734	0.17121	-12.3	24	-1.43328	0.21589	-15.1
First Cmax	24	0.95642	0.25232	26.4	24	0.85625	0.27377	32.0
Ln First Cmax	24	-0.08219	0.29501	-359	24	-0.20600	0.33010	-160
First Tmax (hr)	24	1.13875	0.45716	40.1	24	0.91667	0.35098	38.3

TABLE 1: PHARMACOKINETIC PARAMETERS FOR SERUM CIMETIDINE
LEAST SQUARES MEANS \pm STANDARD ERROR (N =24)
#116-24-11232

fasted

Parameter	Test Perrigo	Reference SmithKline Beech	Test/ Reference	Significance	Study Power	Intrasubject C.V.(%)	90% Confidence Interval
AUC 0-T ($\mu\text{g mL}^{-1}\text{hr}$)	3.806 ± 0.06521	3.679 ± 0.06521	1.03	N.S.	>0.99	8.5	0.99; 1.08
Ln AUC 0-T (Antiln)	1.3209 ± 0.0180 (3.747)	1.2850 ± 0.0180 (3.615)	1.04	N.S.	>0.99	8.8	0.99; 1.08
AUC 0-Inf ($\mu\text{g mL}^{-1}\text{hr}$)	4.216 ± 0.06543	4.066 ± 0.06543	1.04	N.S.	>0.99	7.7	1.00; 1.08
Ln AUC 0-Inf (Antiln)	1.4236 ± 0.0161 (4.152)	1.3875 ± 0.0161 (4.005)	1.04	N.S.	>0.99	7.9	1.00; 1.08
Cmax ($\mu\text{g/mL}$)	1.056 ± 0.03213	0.9776 ± 0.03213	1.08	N.S.	0.98	15.4	1.00; 1.16
Ln Cmax (Antiln)	0.0364 ± 0.0315 (1.037)	-0.0467 ± 0.0315 (0.9543)	1.09	N.S.	0.99	15.4	1.01; 1.17
Tmax (hr)	1.462 ± 0.1245	1.638 ± 0.1245	0.89	N.S.	<0.50	39.0	0.71; 1.08
Rate Constant (hr^{-1})	0.3030 ± 0.00679	0.3143 ± 0.00679	0.96	N.S.	>0.99	10.7	0.91; 1.02
Half-Life (hr)	2.386 ± 0.05352	2.292 ± 0.05352	1.04	N.S.	>0.99	11.2	0.98; 1.10
Cmax/ AUCinf (hr^{-1})	0.2536 ± 0.00624	0.2439 ± 0.00624	1.04	N.S.	>0.99	12.2	0.98; 1.10
Ln (Cmax/AUCinf) (Antiln)	-1.3872 ± 0.0241 (0.2498)	-1.4342 ± 0.0241 (0.2383)	1.05	N.S.	>0.99	11.8	0.99; 1.11
First Cmax	0.9578 ± 0.04670	0.8606 ± 0.04670	1.11	N.S.	0.70	25.2	0.98; 1.24
Ln First Cmax (Antiln)	-0.0822 ± 0.0601 (0.9210)	-0.1994 ± 0.0601 (0.8192)	1.12	N.S.	0.61	30.0	0.97; 1.30
First Tmax (hr)	1.121 ± 0.05979	0.9161 ± 0.05979	1.22	p=0.0240	0.54	28.4	1.07; 1.38

The test of equality of the means, the power of the study to detect a 20% difference in parameters as statistically significant ($\alpha=0.05$), and the 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means from the analysis of variance.

TABLE 5: ADVERSE EVENTS
CIMETIDINE TABLETS, 200 MG
STUDY #116-24-11232

fasted

SUBJECT #	DATE	TIME	EVENT	SEVERITY (1)	RESOLUTION DATE TIME	RELATIONSHIP TO DRUG(2)	RX	PRODUCT UNDER STUDY (3)
3	07/19/97	1949	Increased Diastolic Blood Pressure	1	07/26/97 0553	1	Repeat BP 2X Notified MD	B
	07/26/97	1149	Increased Diastolic Blood Pressure	1	07/26/97 1449	1	Monitor	A
	07/26/97	1700	Toothache	1	UNKNOWN	1	Ice Pack to area	A
22	07/26/97	0900	Upset Stomach	1	07/26/97 0915	2	Monitor	A
23	07/26/97	1720	Headache	1	07/26/97 1915	2	Monitor	A
24	07/19/97	1248	Headache	1	07/19/97 1643	2	Monitor	A

(1) 1=MILD, 2=MODERATE, 3=SEVERE

(2) 1=NO RELATIONSHIP, 2=POSSIBLE, 3=PROBABLE, 4=DEFINITE

(3) A=PERRIGO COMPANY, B=SMITHKLINE BEECHAM

TABLE 1: PHARMACOKINETIC PARAMETERS FOR SERUM CIMETIDINE
LEAST SQUARES MEANS \pm STANDARD ERROR (N =24)
#116-23-11233

fed

Parameter	Test Perrigo	Reference SmithKline Beecham	Test/ Reference	Significance	Study Power	Intrasubject C.V.(%)	90% Confidence Interval
AUC 0-T ($\mu\text{g mL}^{-1}\text{hr}$)	3.391 \pm 0.05289	3.470 \pm 0.05289	0.98	N.S.	>0.99	7.6	0.94; 1.01
Ln AUC 0-T (Antiln)	1.2033 \pm 0.0152 (3.331)	1.2178 \pm 0.0152 (3.380)	0.99	N.S.	>0.99	7.5	0.95; 1.02
AUC 0-Inf ($\mu\text{g mL}^{-1}\text{hr}$)	3.805 \pm 0.05258	3.870 \pm 0.05258	0.98	N.S.	>0.99	6.7	0.95; 1.02
Ln AUC 0-Inf (Antiln)	1.3215 \pm 0.0137 (3.749)	1.3315 \pm 0.0137 (3.787)	0.99	N.S.	>0.99	6.7	0.96; 1.02
Cmax ($\mu\text{g/mL}$)	0.9294 \pm 0.02457	1.003 \pm 0.02457	0.93	p=0.0455	>0.99	12.5	0.87; 0.99
Ln Cmax (Antiln)	-0.0973 \pm 0.0220 (0.9073)	-0.0384 \pm 0.0220 (0.9623)	0.94	N.S.	>0.99	10.8	0.89; 0.99
Tmax (hr)	1.945 \pm 0.1011	1.878 \pm 0.1011	1.04	N.S.	0.71	25.9	0.90; 1.17
Rate Constant (hr^{-1})	0.3191 \pm 0.00588	0.3357 \pm 0.00588	0.95	N.S.	>0.99	8.8	0.91; 0.99
Half-Life (hr)	2.224 \pm 0.03822	2.121 \pm 0.03822	1.05	N.S.	>0.99	8.6	1.00; 1.09
Cmax/ AUCinf (hr^{-1})	0.2453 \pm 0.00444	0.2583 \pm 0.00444	0.95	p=0.0499	>0.99	8.6	0.91; 0.99
Ln (Cmax/AUCinf) (Antiln)	-1.4188 \pm 0.0182 (0.2420)	-1.3699 \pm 0.0182 (0.2541)	0.95	N.S.	>0.99	8.9	0.91; 1.00
First Cmax	0.8900 \pm 0.03215	1.003 \pm 0.03215	0.89	p=0.0215	0.99	16.6	0.81; 0.97
Ln First Cmax (Antiln)	-0.1582 \pm 0.0407 (0.8537)	-0.0392 \pm 0.0407 (0.9615)	0.89	N.S.	0.91	20.1	0.80; 0.98
First Tmax (hr)	1.816 \pm 0.1280	1.844 \pm 0.1280	0.99	N.S.	<0.50	34.3	0.82; 1.15

The test of equality of the means, the power of the study to detect a 20% difference in parameters as statistically significant ($\alpha=0.05$), and the 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means from the analysis of variance.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75285

ADMINISTRATIVE DOCUMENTS

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **75-285** Date of Submission: **December 19, 1997**

Applicant's Name: **L. Perrigo Company**

Established Name: **Cimetidine Tablets USP, 200 mg**

Labeling Deficiencies:

1. UNIT DOSE BLISTER (6s)

Revise the established name to read "Cimetidine Tablets" rather than "Cimetidine Tablet". In addition, we encourage the inclusion of USP in the established name.

3. CARTON (6s)

- a. We encourage the inclusion of "USP" in the established name.

- b. Front Panel

- i. Revise to read "Relieves heartburn, acid...".

- ii. Include the following:

Allergy Warning: Do not use if you are allergic to cimetidine or other acid reducers.

- c. Back Panel

- i. Include the following text after the "Active Ingredient":

Purpose: Acid Reducer.

- ii. Uses

Revise to read:

- **Relieves** heartburn, acid indigestion and sour stomach.

iii. DIRECTIONS

- For relief of symptoms, swallow 1 tablet with a glass of water.
- This product can be used...
- This product should not be given...

iv. WARNINGS

Reverse the order of the fourth and fifth bullets so that "If you have trouble swallowing..." appears first.

- v. Revise to read "This product relieves heartburn...".

- vi. Include the following:

OTHER INFORMATION

Tips for Managing Heartburn

- Do not lie flat or bend over soon after eating
- Do not eat late at night, or just before bedtime
- Certain foods or drinks are more likely to cause heartburn, such as, rich, spicy, fatty, and fried foods, chocolate, caffeine, alcohol, and even some fruits and vegetables
- Eat slowly and do not eat big meals
- If you are overweight, lose weight
- If you smoke, quit smoking
- Raise the head of your bed
- Wear loose fitting clothing around your stomach

4. PATIENT LEAFLET

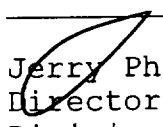
- a. See comment a under CONTAINER.
- b. See comments c i, iii, and iv under UNIT DOSE CARTON.
- c. Revise to read "Percent of Patients with Reduction of Heartburn Symptoms".

[Note: Delete "Prevention"].

Please revise your unit dose blister labels, carton and leaflet labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.


Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Handwritten initials "ISI" and a signature are present above the typed name.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75285

CORRESPONDENCE

L. Perrigo Company
Attention: Brian R. Schuster
117 Water Sreet
Allegan, MI 49010

A standard linear barcode consisting of vertical black bars of varying widths on a white background.

Dear Sir:

NAME OF DRUG: Cimetidine Tablets USP, 200 mg

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 29, 1997

Please identify any communications concerning this application with the ANDA number shown above.

Kassandra Sherrod
Project Manager
(301) 827-5849

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
DETROIT DISTRICT

1560 E. Jefferson Avenue
Detroit, MI 48207-3179
TELEPHONE: 313-226-6260
FACSIMILE: 313-226-3076

February 6, 1998

Mr. Brian Schuster

L. Perrigo Company
117 Water Street
Allegan, MI 49010

Dear Mr. Schuster:

The U.S. Food and Drug Administration (FDA) will be performing Method Verification studies on Cimetidine Tablets USP 200 mg/tab., in connection with your ANDA 75-285. With your cooperation, we can promptly complete this portion of our evaluation of your application.

In order to perform the necessary testing, please provide us with a sample from the reserve portion of the lot used to establish the bioequivalence or bioavailability of your product. Ideally, this sample should be within the proposed expiration date. If it is beyond this date and there is another pre-approval batch within expiration, send that instead. If, however, a batch not in the ANDA is used, the batch record and Certificate of Analysis must be submitted as an unsolicited amendment to the application.

The sample should consist of the following:

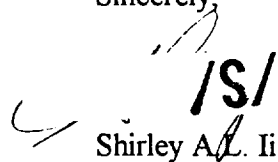
1. Cimetidine USP Reference Standard
2. Cimetidine Tablets 200 mg/tablet, 6 count blister strips, 50 units
3. The latest test methods, including assay for the active ingredient, impurities or related substances, identification tests and specifications.
4. A copy of the worksheets for the analysis of the same lot with the calculations, results and associated spectra and chromatograms.

Please forward these materials within ten days of receipt of this letter via express or overnight mail to the Detroit District Laboratory, 1560 East Jefferson Avenue, Detroit, MI 48207, Attn: Shirley A.L. ii ANDA Team Leader.

Page 2
February 6, 1998

Thank you, in advance, for your cooperation. Please do not hesitate to call or FAX me if you have any questions. Telephone (313) 226-6260 Ext. 166 or FAX 3132263076.

Sincerely,


Shirley A. Li

cc: William P. Rickman, Reviewer, OGD HFD-615
Melvin Robinson, Pre-Approval Manager, Detroit District HFR-CE760
NDA/ANDA File



OK. to file
S. Middelton
1-21-98

December 19, 1997

Douglas Sporn, Director
FDA, CDER, OPS, Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**RE: Abbreviated New Drug Application
Cimetidine Tablets, 200 mg
Over-the-Counter Drug Product**

Dear Mr. Sporn:

The L. Perrigo Company is submitting for your review and approval, an ANDA for **Cimetidine Tablets, 200 mg** pursuant to 505(j) of the Federal Food, Drug, and Cosmetic Act. Perrigo's **Cimetidine Tablets, 200 mg** is identical in strength, indications, active ingredient, route of administration and dosage form to SmithKline Beecham's Tagamet HB® 200 product.

Tagamet HB® 200 (NDA #20-238) is listed in the Seventeenth Edition of Approved Drug Products with Therapeutic Equivalence Evaluations as an OTC drug with no patent protection and two market exclusivities. A "new strength" which expires on June 19, 1998; and "prevention of meal-induced heartburn" which expires on November 15, 1998. The labeling of the proposed drug will not include the prevention of heartburn claim if marketed prior to November 15, 1998.

A paragraph I patent certification is enclosed in Section 3. Bioequivalence studies conducted under fasted & fed conditions, sponsored by Perrigo, are also included in this ANDA.

Attached is an additional copy of this cover letter. Please stamp the date of receipt on it and return to me in the attached self-addressed stamped envelope.

Should you require additional information, please contact me directly by telephone at 616-673-9745, by FAX at 616-673-7655 or the address on this letterhead.

Respectfully submitted,

Brian R. Schuster
Regulatory Affairs Manager

RECEIVED

DEC 29 1997

GENERIC DRUGS



December 19, 1997

Mr. John Dempster
Director, Compliance Branch
Food & Drug Administration
1560 Jefferson Avenue
Detroit, MI 48207

**RE: Abbreviated New Drug Application
 Cimetidine Tablets, 200 mg**

Dear Mr. Dempster:

The Perrigo Company has submitted by Federal Express an Abbreviated New Drug Application for **Cimetidine Tablets, 200 mg**, dated December 19, 1997.

As required by 21 CFR 314.94(d)(5), the Perrigo Company has enclosed a true copy of this ANDA (including a copy of the 356h form). Perrigo certifies that the ANDA contained in this "field copy" is a true copy of the technical sections of the ANDA which was submitted to the FDA headquarters.

Respectfully submitted,

A handwritten signature in cursive script, appearing to read 'Brian R. Schuster'.

Brian R. Schuster
Regulatory Affairs Manager

cc: G. Boerner
 D. Jespersen



*Noted by
9/25/98*

September 18, 1998

Office of Generic Drugs, OPS, CDER, FDA
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attention: Mr. Douglas Sporn, Director

FPL

FACSIMILE AMENDMENT

NEW CORRESP

NC

**RE: Cimetidine Tablets, USP, 200 mg
ANDA 75-285**

Dear Mr. Sporn:

This Facsimile Amendment is in response to the letter of comments received from the Office of Generic Drugs, Division of Labeling and Program Support, dated September 17, 1998, regarding the L. Perrigo Company's Cimetidine Tablets, USP, 200 mg, application.

We hereby amend ANDA 75-285 to address the comments in the September 17, 1998, correspondence. Because of the nature of the request, i.e., to submit one-piece final printed labeling, the cover letter of this amendment is being submitted by fax, with the complete amendment following by express mail service (FedEx) to arrive on September 21, 1998.

Enclosed are 12 copies of the one-piece, dual sided, final printed consumer information leaflet. The leaflet has not been revised in any way from that submitted for review in the August 19, 1998, amendment. In accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of the insert was submitted in the August 19, 1998, amendment.

We note that FDA reserves the right to request further changes in labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

If you have any questions or require additional information, please feel free to contact me by telephone at 616-673-9745, or by fax at 616-673-7655.

Sincerely,

Brian Schuster
Manager, Regulatory Affairs

RECEIVED

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*Madine
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